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Short commentary on NDMA (N-nitrosodimethylamine) contamination of valsartan products

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ABSTRACT

A range of generic valsartan products have been found to be contaminated with nitrosamines (principally N-nitrosodimethylamine; NDMA). We present information and discuss various elements of this phenomenon including: actions taken by regulatory agencies, source of the nitrosamine impurities, range of possible risk assessments based mainly on ICH M7 criteria, epidemiological assessment and analytical aspects.

1. Introduction

Many observers, across Industry and within the various world wide regulatory agencies had assumed that control of mutagenic impurities in pharmaceuticals was a "done deal and reduced to practice" (Elder, 2018). The guidance for the control of mutagenic impurities (ICH M7[2]) was first introduced during 2014 and subsequently updated at the beginning of 2017 (ICH M7(R1)[3]). Robust, risk based processes to assess the possibility for mutagenic impurity formation (real and potential) and control were in place across industry. It was surprising to many therefore, that in the middle of 2018, EMA (European Medicines Agency) announced it was "reviewing medicines containing valsartan drug substance supplied by Zhejianjg Huahai following the detection of an impurity" (EMA, 2018a). [Valsartan (see Fig. 1 for structure) is an angiotensin II receptor antagonist used to treat a number of conditions, mainly high blood pressure and congestive heart failure, with a maximum daily dose of 320 mg] The product recall (Christensen, 2018) involved nearly 2300 batches that had been despatched to Germany, Norway, Finland, Sweden, Hungary, the Netherlands, Austria, Ireland, Bulgaria, Italy, Spain, Portugal, Belgium, France, Poland, Croatia, Lithuania, Greece, Canada, Bosnia and Herzegovina, Bahrain and Malta. EMA indicated that the impurity of concern (N nitrosodimethylamine; NDMA) had formed as "a result of a change in the manufacturing process" (Christensen, 2018). In September 2018, EMA (EMA, 2018b) stated: "Medicines containing valsartan made by Zhejiang Huahai in China have been recalled by national authorities. Medicines containing valsartan from another company Zhejiang Tianyu are no longer being distributed in the EU." In July 2018 the Danish Medicines Agency (Danish Medicines Agency, 2018) recalled a variety of valsartan containing products although no information on NDMA levels was provided. On the other hand in October 2018, FDA (FDA, 2018a) listed 8 valsartan containing products for which NDMA content ranged from 0.3 to 20 μg/tablet (see Table 1). [Note that recalls have applied only to some generic valsartan products; the originator product Diovan appears not to be affected.] FDA recently released information on several valsartan products contaminated with NDEA (N nitrosodiethylamine) (FDA, 2018b).

N Nitrosodimethylamine (see Fig. 2)(NDMA; CAS no 62 75 9) is described by the IARC (International Agency for Research on Cancer) as genotoxic, carcinogenic in multiple rodent and nonrodent animal species and so "should be regarded for practical purposes as if it were carcinogenic to humans". To the best of our knowledge, this was the first instance of a product recall being initiated on the basis of an N nitroso impurity, which, according to ICH M7 [Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk], is a member of the so called "cohort of concern" class of high potency mutagenic carcinogens (ICH M7, 2014; ICH M7(R1), 2017).

2. ICH M7 guideline on mutagenic impurities

ICH M7 incorporated a concept first introduced by the Safety Working Party (SWP) in the EU guideline on genotoxic impurities. This is the threshold of toxicological concern (TTC) initially developed in the context of food safety (Kroes et al., 2004). The TTC thereby defined an appropriate intake (or risk) for any chemical with limited or no supporting safety data that would pose "a negligible risk of carcinogenicity or other toxic effects". A TTC value of 1.5 μg/day, which corresponds to

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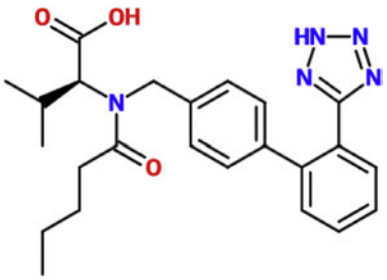

Fig. 1. Structure of valsartan.

Table 1
Typical levels of NDMA Contamination in Valsartan tablets (FDA, 2018a).

Supplier	Product	NDMA Levels (μg/tablet)
Prinston Pharma	Valsartan 320 mg tablets	15–16
Prinston Pharma	Valsartan 320mg/HCTZ 25 mg tablets	13–20
Torrent Pharma	Valsartan 320mg/Amlodipine 10mg/HCTZ 25 mg	10–12
Torrent Pharma	Valsartan 320mg/Amlodipine 10 mg	5–9
Teva Pharma	Valsartan 320 mg tablets	8–17
Teva Pharma	Valsartan 320mg/HCTZ 25 mg	7–10
Hetero Labs Ltd	Valsartan 320 mg tablets	0.3–0.4

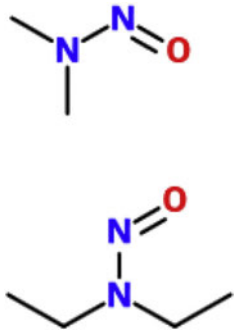

Fig. 2. Structure of N-nitrosodimethylamine (NDMA) and N nitrosodiethylamine (NDEA).

a theoretical 10^{-5} excess lifetime risk of cancer was adopted, whereas the cancer TTC for foodstuffs is 0.15 μg/day based on a risk of 10^{-6} (ICH M7, 2014). ICH M7 mentions a number of important caveats including: (a) the TTC is a highly hypothetical concept that should not be regarded as a realistic indication of the actual risk; (b) exceeding the TTC is not necessarily associated with an increased cancer risk given the conservative assumptions employed in its derivation: (c) The implied concern levels represent a small theoretical increase in risk when compared to human overall lifetime incidence of developing any type of cancer, which is greater than 1 in 3; (d) any exposure to an impurity that is later identified as a mutagen is not necessarily associated with an increased cancer risk for patients already exposed to the impurity. Distinct from guidance on foodstuffs (which applies to genotoxic impurities), ICH M7 restricts the application of the cancer TTC concept to DNA reactive (mutagenic) carcinogens; an experimental or predicted positive result in the Ames' test is employed as an epigone of DNA reactivity. Interestingly, although the derivation of the cancer TTC is acknowledged to be highly conservative, non transparent and compromised by several methodological flaws (Boobis et al., 2017; Snodin, 2018a), neither ICH nor EMA has subsequently undertaken any re evaluation.

Some structural groups were identified to be of such high potency that intakes even below the TTC could theoretically be associated with a potential carcinogenic risk. This group of high potency mutagenic carcinogens referred to as the "cohort of concern" (COC), comprises aflatoxin like , N nitroso , and alkyl azoxy compounds; benzidine derivatives might also usefully be included. Industry had always argued that the "cohort of concern" structural classes were very unlikely to be encountered during the routine synthesis of pharmaceutical drug substances. Delaney (2007) highlighted that the TTC was, "(a) unduly influenced by many classes of potent carcinogens of historic concern which would be impossible to generate unknowingly as pharmaceutical impurities, and (b) that the majority of reactive chemicals that would be useful to synthetic chemists are among the least potent carcinogens in the underpinning supportive analyses". Indeed, the N nitroso structural class is significantly over represented in the compound libraries that underpin the TTC, with over 100 N nitroso compounds, ca. 14% being present in the Kroes (Kroes et al., 2004) (105/730), and Cheeseman (Cheeseman et al., 1999) (101/706)) databases. If carcinogenic potency data are available, as is the case for NDMA and many other N nitrosamines in the CPDB (Carcinogenic Potency Database) (The Carcinogenic Potency, 2018), it is possible to determine compound specific acceptable intake (AI) limits using established methodology (ICH M7(R1), 2017; Snodin, 2010).

3. Recalls on sartans Contaminated with N-Nitrosoamines

As such, a product recall based on a "cohort of concern" impurity, i.e. NMDA, that appeared to be "unknowingly generated", was extremely worrying. The initial EMA (EMA, 2018a) recall was rapidly followed by FDA product recalls (FDA, 2018c) and similar actions in India (Mukherjee, 2018). By the end of August 2018, valsartan drug substance from 16 different suppliers to the US market had been implicated (FDA, 2018d). Then EMA extended the review to include other sartans (candesartan, irbesartan, losartan and olmesartan) prompted by the detection of very low levels of N nitrosodiethylamine (NDEA) (see Fig. 2) in another active substance, losartan, made by Hetero Labs in India (FDA, 2018d). Subsequently, NDEA was also detected in some of the recalled valsartan products (EMA, 2018c). Overall, it seems that NDMA or NDEA has been detected in valsartan (and other related sartans) produced by several API manufacturers, but the extent and duration of patient exposure to these contaminants is not completely clear.

4. Changes to synthetic routes

A key question is "How was Valsartan contaminated with NDMA?" (Perscheid, 2018; Shanley, 2018). Zhejianjg Huahai modified the existing chemistry during the period between 2011/2013 (Perscheid, 2018; Shanley, 2018) by replacing tributyltin azide with the more reactive sodium azide as a reagent used in the formation of a tetrazole ring structural moiety, which necessitated the introduction of $NaNO_2$ to remove excess azide reagent (Shanley, 2018). However, under acidic conditions nitrite can also form nitrous acid. It would appear that impurities in the solvent DMF (dimethylformamide) particularly dimethylamine, but also diethylamine, reacted with nitrous acid (a nitrosating agent) to yield NDMA (or NDEA). [It should be noted that the presence of other nitrosamines originating from synthetic intermediates/impurities cannot be totally excluded.] Regulatory questions now appear to be focused on this mechanistic explanation and all sartans that contain a tetrazole ring, particularly if there is potential for nitrosation of a secondary amine during synthesis, are under investigation.

Several observers have been highly critical of both the companies concerned and the regulatory oversight, indicating that "if Zhejianjg Huahai did not identify the need to develop a control strategy to reduce the new risks introduced with the optimized process, neither did the regulators when they approved the process change" (Shanley, 2018). However, it is easy to be critical after the event. Possibly the biggest issue is that knowledge of parts per million (ppm) chemistry is still very

much in its infancy. As such, what appears to have been lacking in the risk assessment procedure from the various companies wasn't a lack of awareness of diazonium generating reactions e.g. Sandmyer, Gomberg Bachmann, Balz Schiemann or in this particular case the use $NaNO_2$ to destroy excess sodium azide; it was the potential presence of aliphatic secondary amines arising as solvent impurities (Allmendinger et al., 2012), thus permitting the formation of N nitrosamine by products (Oruganti, 2018). In retrospect, this possibility should also have been highlighted during the risk assessment process. EU regulators (Anderson, 2016; CPMP/CVMP, 2013) in particular, have long identi fied the potential presence of the class I solvent benzene as a con taminant in several other common solvents, e.g. toluene, acetone and short chain alkyl alcohols, e.g. methanol, ethanol (Gray, 2018). It is disappointing that the risk assessment failed to identify aliphatic amines as potential impurities in DMF, particularly under harsh, forcing conditions. It would appear likely that potential drug substance im purities generated from impurities in reagents (including solvents) might feature more prominently in future regulatory deficiency ques tions.

5. Risk assessment for NDMA

It seems reasonable to ask what constitutes a virtually safe dose (VSD) for NDMA, particularly as the substance is a known environ mental contaminant that is routinely found in foodstuffs (including cured meats, dairy products and certain vegetables) and drinking water. Intake levels range from 0.0004 to 0.23 μg in cured meat, 0.0004 1.02 μg in smoked meat, 0.0006 0.13 μg in grilled meat and 0.07 0.07 μg in bacon (FDA, 2018c). Based on a daily consumption of ca. 20 g of processed meat per day, Danish researchers found that this resulted in a daily of exposure for adults of 33 ng kg/bw/day of non volatile nitrosamines and 0.34 ng kg/bw/day of volatile nitrosamines (the latter class would include NDMA and NDEA) (Herrmann et al., 2015). NDMA can also be formed endogenously following consumption of nitrate containing foodstuffs (Zeilmaker et al., 2010). NDMA is an unintended by product of the chlorination of waste waters and drinking waters in chemical processes that use chloramines as the disinfecting agent (Technical fact sheet: N n, 2014). Inhalation and/or dermal ex posure can occur in several industries (N fa, 2018). FDA has indicated that levels of NDMA up to 0.096 μg/day, i.e. 0.1 μg/day are safe, which is equivalent to 0.3 ppm (0.096 × 1000/320) in Valsartan tablets (FDA, 2018d). A compound specific assessment using ICH M7(R1)[2,3] metho dology also produces a value of 0.096 μg/day for whole lifetime ex posure based on the CPDB harmonic mean TD_{50} of 0.096 mg/kg/day (N nitrosodimethylamine, 2018). Another risk assessment by Fitzgerald and Robinson based on a comprehensive lifetime liver cancer dose re sponse study in rats (listed in the CPDB) produced a TDI (tolerable daily intake) in the range 0.2 0.6 μg/day, based on a bodyweight of 60 kg (Fitzgerald and Robinson, 2007). Since exposure via pharmaceuticals is unlikely to last more than a few years the ICH M7[2,3] less than lifetime (LTL) approach can be applied to the most conservative value of 0.096 μg/day resulting in limits of 10/1.5 × 0.096 = 0.64 μg/day if exposure is ≤ 10 years and 20/1.5 × 0.096 = 1.28 μg/day if exposure is ≤ 1 year (Snodin, 2018b). Assuming that use of existing supplies of potentially contaminated valsartan is sanctioned by regulatory autho rities for up to one year then the above risk assessment would lead to a limit of 4.0 ppm (1.28 × 1000/320) NDMA in valsartan.

Alternative risk assessment metrics are permitted under ICH M7 (R1)[2,3] which states: ".other established risk assessment practices such as those used by international regulatory bodies may be applied either to calculate acceptable intakes or to use already existing values pub lished by regulatory authorities." One such alternative metric, some times called "reference point" or "point of departure POD" is the $BMDL_{10}$ benchmark dose lower bound corresponding to a 10% in crease in tumour incidence (EFSA Scientific Committee, 2016). Spe cialist software is available that enables modelling of dose response producing a fitted dose response model and estimation of BMDs (small but measurable treatment related changes, usually set at 5 or 10%) with confidence intervals. When dealing with genotoxic/carcinogenic im purities, EFSA (European Food Safety Authority) has concluded that: "a margin of exposure of 10,000 or higher, if it is based on the $BMDL_{10}$ from an animal carcinogenicity study, and taking into account overall uncertainties in the interpretation, would be of low concern from a public health point of view", where margin of exposure (MOE) is the ratio of $BMDL_{10}$ to estimated consumer intake. In relation to NDMA, SCCS (Scientific Committee on Consumer Safety) has determined a $BMDL_{10}$ of 27 μg/kg/day (Scientific Committee on Consumer Safety, 2012), equivalent to 1620 μg/day in a 60 kg consumer. Survey data from The Netherlands and Finland indicate that adult dietary exposure to NDMA from food and beverages is around 0.1 μg/day, thus providing a MOE of 16200 (> 10,000) based on the SCCS's reference point. With no estimation of other sources of NDMA (such as drinking water, smoking, endogenous production) this assessment should be regarded as somewhat provisional in relation to an evaluation of total NDMA exposure. On the other hand, since some valsartan products may con tain up to 20 μg NDMA in a daily dose (see Table 1), the resulting MOE for lifetime exposure is ≥ 81 and ≥ 1077 for exposure of duration up to one year.

6. Danish epidemiological study

In a recent publication, Pottegård et al. (2018) have reported on the outcome of a Danish nationwide cohort study assessing the risk of cancer from valsartan products potentially contaminated with NDMA. The final cohort comprised 5150 people followed for a median of 4.6 years. The authors assumed that as the valsartan process changes were made during the period of 2012/2013, that all subsequent drug product supplied from Zhejianjg Huahai would be contaminated with NDMA, i.e. between September 2011 and June 2017, which does run the risk of over estimating the affected patient group. With 104 cancer outcomes among NDMA unexposed participants and 198 among exposed parti cipants, the adjusted hazard ratio for overall cancer was 1.09 (95% confidence interval 0.85 to 1.41), with no evidence of a dose response relation (P = 0.70). For single cancer outcomes, increases in risk were observed for colorectal cancer (hazard ratio 1.46, 95% confidence in terval 0.79 to 2.73) and for uterine cancer (1.81, 0.55 to 5.90), al though with wide confidence intervals that included the null. Although the results are reassuring, the authors (Pottegård et al., 2018) re commend that studies with extended follow up are needed to assess long term cancer risk.

7. Analytical methods

Interestingly, the LOQs/LODs of the various methods published by European and US regulators are not all aligned with the VSD limit of 0.1 μg/day mentioned above. This is worrying in relation to the ana lytical target profile (ATP). The ATP is defined as a "prospective sum mary of method objectives, and method controls and their pre defined acceptance criteria (which are method independent) collectively called quality requirements, to ensure the uncertainty of the reportable result is controlled to a level the method is performing for its intended pur pose, i.e. the adequate measurement of the quality attributes (QAs) of the drug product" (Kizhakkedathu, 2017).The original HS GC MS (single quad) method developed by FDA for the presence of NDMA in APIs is aligned with the pre defined acceptance criteria (i.e. the VSD) and cites an LOQ of 0.3 ppm (FDA, 2018e); whereas, the combined HS GC MS (single quad) for both NDMA and NDEA also developed by the FDA is more sensitive and has LOQ limits of 0.1 and 0.05 ppm, re spectively (FDA, 2018f). It isn't clear why increased sensitivity is re quired. Analytical limits of one third of the VSD are typically used if a company wants to remove determination of a mutagenic impurity from routine specification testing (ICH M7, 2014; ICH M7(R1), 2017); but in

Table 2
Summary of CHMP preliminary assessment report on sartans containing a tetrazole group.

Issue	CHMP Comment
Background	Referral under Article 31 of Directive 2001/83/EC. Initially a benefit-risk assessment of NDMA contamination in valsartan; later extended to other tetrazole-containing angiotensin-receptor blockers (ARBs) such as candesartan, irbesartan, losartan, olmesartan, and other N-nitrosamines.
Cause of nitrosamine formation	Principal root cause considered to be nitrosation of secondary (and tertiary) amines present as residual reagents, impurities in DMF or breakdown products of drug substances (such as valsartan).
Analytical methods and results	Several methods have been developed by OMCLs typical LoQs being 0.2 and 0.04 ppm for NDMA and NDEA respectively. Some batch-to-batch variability in levels of N-nitrosamines has been noted as well as discrepancies between levels in drug substances and the corresponding drug products. No evidence for significant contamination of candesartan, irbesartan, losartan, olmesartan with NDMA or NDEA although N-nitrosamine contamination is possible in theory based on the routes of synthesis. Mean NDMA concentrations in valsartan drug substance ranged from 41-71 ppm across 4 OMCLs. Mean values reported by manufacturers for NDMA in valsartan were within this range and concentrations > 1 ppm NDEA (11.9 and 1.9) were found for only two batches of API.
Estimates of patient exposure	NDMA in valsartan: maximum duration 6 years at a max average daily exposure of 24 μg; NDEA in valsartan: max duration 4 years at a max average daily exposure of 3.7 μg. Data on co-contamination are limited.
Toxicological assessment	NDMA: A compound-specific AI of 96ng/day (equivalent to 0.3 ppm in a valsartan tablet of strength 320 mg) was calculated by linear extrapolation of the harmonic-mean TD_{50}. Over 6 years the acceptable intake is determined to be 1.12μg/day (cancer risk level 1 in 100,000) which was set as a regulatory action level (RAL). The max average daily exposure of 24μg corresponds to a theoretical excess lifetime cancer risk level of 1 in 5000. Risk assessments based on the $BMDL_{10}$ for NDMA resulted in RALs ranging from 1.12 to 2.5μg/day. NDEA: An AI of 26.5ng/day was determined, equivalent to 0.083 ppm in a 320-mg tablet of valsartan. Over 4 years this AI corresponds to an average of 0.46μg/day and theoretical excess lifetime cancer risk level of 8 in 100,000.
Toxicological mechanisms	NDMA is thought to be activated initially by CYP2E1 (NDEA by CYP2E1 and CYP2A6) followed by other reactions to form methyldiazonium ion as the proximate mutagen/carcinogen.
Additional nitrosamines	DIPNA (N-nitrosodiisopropylamine), EIPNA (N-nitrosoethyldiisopropylamine) and NAP 181-14 [(S)-2-(((2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)(nitroso)amino)-3-methylbutanoic acid] (N-nitrosovalsartan), have been detected in some valsartan batches. These nitrosamines are of unknown carcinogenic potential but are likely to be of lower potency than NDMA/NDEA.
Other related risks	Assurance needs to be provided that sodium azide (highly reactive and mutagenic, although negative in existing carcinogenicity bioassays), which is used as a reagent, is appropriately purged and is absent from the valsartan API or it should be controlled as part of the API specification
Risk minimisation/avoidance	If possible syntheses that contain any potential nitrosamine-generating step should be avoided.
Clinical assessment	Sartans are important for the treatment of severe cardiovascular disease and are in widespread use. A worst-case scenario where none of the tetrazole-ARBs, e.g. candesartan, irbesartan, losartan, olmesartan and valsartan, were available would pose a challenge to treating physicians. Non-tetrazole ARBs, e.g. azilsartan, eprosartan and telmisartan, ACE-inhibitors, and other drugs approved in the therapeutic areas (arterial hypertension, heart failure, cardiovascular prophylaxis, renal disease in special populations) may serve as therapeutic alternatives in most cases.

this case it would be inconceivable that regulators would allow “skip lot” testing approaches for impurities as toxic as NDMA or NDEA. Similarly, within Europe several OMCLs (official medicines control laboratories) have developed methodologies for these analytes. PALG (Public Analyst's Laboratory in Galway) developed an HPLC UV analysis (PALG (Public Analyst's Laboratory in Galway), 2018), for the presence of NDMA in APIs and sartan tablets, with an LOQ of 0.3 ppm; whereas, ANSM (French National Agency for Medicines and Health Products Safety) has developed an HS GC MS (single quad) method for the presence of NDMA in APIs and sartan tablets (ANSM (French National Agency for Medicines and Health Products Safety), 2018). Method B uses a standard addition plot for NDMA (0, 2, 4 and 6 ppm); whereas, method C has an LOD of 0.04 ppm (ANSM (French National Agency for Medicines and Health Products Safety), 2018). Finally, CVUA's (Chemisches und Veterinäruntersuchungsamt) method uses APCI UHPLC MS/MS to both detect and quantify NDMA in drug products.[43] A standard addition plot for NDMA (0.1 3 ppm) is used and the LOQ is 0.2 ppm. It does seem rather illogical for these methods not to identify the VSD (as a ppm equivalent) for the analyte(s) in question and more importantly be aligned with one another since the pre defined acceptance criteria should be the same. In these circumstances, there are no benefits for developing methods that are too sensitive for the given task and consequently may be non robust, i.e. not fit for purpose. No validation data are provided to demonstrate that these methods are indeed fit for purpose and can routinely achieve the requisite sensitivity, although FDA does indicate that the “method should be validated by the user if the resulting data are used to support a required quality assessment of the API or drug product, or if the results are used in a regulatory submission” (FDA, 2018e; FDA, 2018f).

8. Guidance to patients

The levels of NDMA in different Valsartan products (FDA, 2018a), including several combination tablets exceed the VSD (of 0.1 μg/day) set by FDA. Products from most suppliers exceed the proposed VSD limit by a considerable margin (Table 1). On the other hand, FDA advised patients to “continue taking your current medicine until your doctor or pharmacists gives you a replacement or a different treatment option. Untreated hypertension (high blood pressure) leads to an increase in the risk of heart attacks and stroke. Untreated heart failure increases the risk of hospitalization and death” (FDA, 2018a). This obviously implies that FDA views maintenance of treatment to be more important than exposure to a probable carcinogen that is likely to be encountered as part of a diet particularly one that contains an excessive amount of cured meat. These recommendations appear to be aligned with data from the recent comparative Danish epidemiological study (Pottegård et al., 2018).

9. CHMP preliminary assessment report on N-Nitrosamine contaminants in sartans

Following a Referral under Article 31 of Directive 2001/83/EC, in late November 2018 CHMP (EU Committee for Medicinal Products for Human Use) released a preliminary assessment report (EMEA/H/A 31/1471) on “Angiotensin II receptor antagonists (sartans) containing a tetrazole group medicinal products” (CHMP, 2018). The main purpose of the CHMP review was to evaluate the benefit risk for such sartan products given the presence of previously undetected N nitrosamine impurities and to advise whether the marketing authorisations of these products should be maintained, varied, suspended or revoked. The principal findings are summarized in Table 2.

The toxicological part of the assessment was contributed by the CHMP Safety Working Party (SWP) and it is appears that the SWP’s determination of RALs (regulatory action limits) is not fully compliant with ICH M7 methodology. Using NDMA as an example, SWP calculated the total cumulative permissible exposure over 70 years based on

the acceptable intake (AI) of 96ng/day. This is equivalent to 25550 x 0.096 = 2453 μg. Assuming that this total exposure could occur over 6 years, dividing by the number of days in 6 years (2190) produces an RAL of 1.12μg/day. Our approach uses the same AI but determines an RAL by application of the appropriate LTL (less than lifetime) factor (10/1.5) to produce a lower value of 0.64μg/day. For NDEA, based on an AI of 26.5ng/day use of the standard ICH M7 methodology produces a 1 10 year RAL of 0.18μg/day (versus the CHMP's 4 year value of 0.46μg/day). [Application of the SWP's methodology based on Haber's rule would revolutionize ICH Q3A (R2) guidance on non mutagenic impurities. For example a drug substance with maximum daily dose of 100 mg has a qualification threshold of 0.15% equivalent to 150μg/day. Over 70 years a cumulative exposure to a non mutagenic impurity present at the qualification threshold in this drug substance of 25550 x 0.15 = 3932.5 mg would be considered acceptable. Based on an exposure period of 6 years this amount of impurity is equivalent to 3932.5/2190 = 1.8 mg/day, nearly 12 times the Q3A based limit.]

10. Conclusions

On the whole the issue of valsartan (and related sartans) recalls has been handled in a professional and objective manner by regulatory agencies (RAs) and patients have been appropriately advised on the relative benefits of continuing their medication versus the potential increased risk of cancer. Data on N nitrosamines in sartans are still being gathered and evaluated by RAs and so complete resolution of the various issues involved could take a considerable time.Unfortunately, some commentators are still intent on raising spectres of undetected mutagenic impurities in common medications, without any balanced benefit/risk perspective. Speculative hypotheses regarding the potential presence of epichlorohydrin in levocarnitine and 1 chloro 4 nitrobenzene in acetaminophen (paracetamol) (Shanley, 2018), without providing any evidence that they would be present or explaining why the downstream purging of these reactive chemicals would not effectively remove them prior to the final isolation/crystallisation stages, are not helpful. It would also be useful if the VSD for these mutagenic analytes were more fully aligned with the method's pre defined acceptance criteria. Currently, this isn't the case which causes unnecessary confusion.

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